REMARKS

Claims 1-29 have been cancelled without prejudice. Claims 30-41 are pending.

In the interest of expediting reconsideration and allowance, Claim 31 is amended to further clarify that the fusion proteins are not natural HBV surface proteins as is described in the specification. Support for this amendment can be found in original claims 1 and 2, as well as in the specification at page 3, last paragraph, and the paragraph bridging pages 4 and 5, particularly the first three lines of page 5. No new matter is added by this amendment. Entry of the amendment and reconsideration is respectfully requested.

Claim Rejections under 35 U.S.C. §112.

Claims 30-41 stand rejected under the first paragraph of 35 U.S.C. §112 for alleged lack of enablement for all of the peptides "in the genus of claim 30 or fusion proteins that comprise the motif". This rejection is unwarranted. The Office Action states, on page 4, that only one of the polypeptides in claim 30 has been shown to function as a fusion protein. To the contrary, two of the ten (i.e., 20 %) polypeptides encompassed by claim 30 (SEQ ID NO: 2 and SEQ ID NO: 10) are shown in the specification to enhance cell permeability when fused to another polypeptide.

Example 1, on page 9 of the specification, shows that the polypeptide of SEQ ID NO: 2 (i.e., the peptide shown in Figure 1) when fused to the PLAP motif from the cytoplasmic domain of TNF-RI allows this protein to enter the cell and inhibit the activation of C-Raf1 kinase (see the results in Figure 2). A fusion protein of SEQ ID NO: 2 with a mutated (inactive) PLAP motif (i.e., the KLAP motif) was also prepared. In addition, Example 4 on pages 13-14 shows that a polypeptide of SEQ ID NO: 10 ("DHBV residues 42-53" in Figure 4), when fused to enhanced green fluorescent protein (eGFP) was transported into a cell.

It should be noted that the amino acid sequences of the peptides used in the working examples, i.e., SEQ ID NO: 2 and SEQ ID NO: 10, are completely different. The commonality between these two sequences and each of the eight other peptides of claim 30 is that these peptides each have substantially the same hydropathy profile. The three peptides of claim 39 (i.e., SEQ ID NO: 4, 6, and 8) are all minor variants of SEQ ID NO: 2, and each also has the same hydropathy profile as SEQ ID NO: 2 (see Figures 3A and 3B). The three peptides of claim 40 (i.e., SEQ ID

NO: 9, 10, and 11) are all segments of avian hepadnaviruses, and also share the same hydropathy profile as SEQ ID NO: 2. Similarly, the two peptides of claim 41 (i.e., SEQ ID NO: 12 and 13) are each fragments of rodent hepadnaviruses, and share the same hydropathy profiles as SEQ ID NO: 2, as well (see Figure 5).

There is no requirement in patent law that every species in a Markush group be supported by a working example. In the present application there are working examples encompassing 20% of the peptides in claim 30 and 33% of the peptides of claim 40. The commonality between the sequences of the peptides used in the working examples (SEQ ID NO: 2 of claim 30, and SEQ ID NO: 10 of claims 30 and 40) is the hydropathy profile of the peptides. The specification, on page 2, teaches that it is the hydropathy profile that imparts the cell permeability enhancing activity to the peptides. The fact that both SEQ ID NO: 2 and SEQ ID NO: 10 are active at providing cell permeability despite great differences in their amino acid sequences bolsters the teachings of the present application that the hydropathy profile is the controlling factor in the cell permeability enhancing activity of the peptides of the invention. Accordingly, the specification clearly provides enabling support for claims 30, 39, 40, and 41.

With respect to claims 31-38, which are directed to fusion proteins, the specification provides three working examples of such fusion proteins, as noted above. Furthermore, the specification provides a lengthy description of the various polypeptides that can be fused to the cell permeability enhancing peptides in the fusion proteins of the invention (see e.g., page 4). Accordingly, the present specification provides sufficient teachings to have enabled one of ordinary skill in the art, at the time the application was filed, to successfully prepare the presently claimed fusion proteins.

In addition, the inventors have published an article in the journal, *Gene Therapy*, vol. 7, pp. 750-758 (2000), a copy of which is transmitted herewith, in which additional examples of fusion proteins of SEQ ID NO: 2 (e.g., a fusion protein of SEQ ID NO: 2 with eGFP, a fusion protein of SEQ ID NO: 2 with His_6-tagged PreS2, and a fusion protein of SEQ ID NO: 2with His_6-tagged PreS1- PreS2) were prepared according to the invention. This paper demonstrates that the fusion proteins were capable of being transported across cell membranes into plant cells, as well as

mammalian cells (see 754, col. 2). Furthermore, the article shows that transport by fusion proteins comprising SEQ ID NO: 2 can occur *in vivo* in rats (see pg. 755, col. 1).

WO 00/46376 (a copy of which is transmitted herewith, along with an English language translation) provides an even more dramatic example of a fusion protein of the invention. In WO 00/46376, protein particles comprising a fusion protein of SEQ ID NO: 2 with an HBcAg protein and a fibronectin binding site, and having a DNA molecule encapsulated within the fusion protein were prepared. In this example, not only was the protein transported into the cell, but also the encapsulated DNA (see, e.g., the English translation, pg. 1, line 21 through pg. 2, line 15; as well as pg. 3, line 33 through pg. 4, line 32 and the examples on pages 7 through 11).

Each of the examples in the *Gene Therapy* article and in WO 00/46376 follow the teachings of the present application to successfully provide fusion proteins that transport across cell membranes. The fusion partners for the fusion proteins that have been made according to the invention vary greatly in size and function, and include green fluorescent protein, the PLAP motif from the cytoplasmic domain of TNF-RI, and a complex comprising a protein and DNA. The results presented in these documents are in accord with the teachings of the present application. The rejection of claims 30-41 for lack of enablement should be withdrawn.

Claims 31-41 also stand rejected under the first paragraph of 35 U.S.C. §112 for allegedly lacking a written description that would have conveyed to one of ordinary skill in the art that the inventors had possession of the claimed invention. However, the Office Action erroneously states on page 4, that "applicants have only disclosed the sequence identified as SEQ ID NO: 4 [sic] (DHBV) which is directed to the cell permeability peptide (CPP) linked to a second polypeptide (Example 4)." In fact the sequence of the DHBV peptide of Example 4 is SEQ ID NO: 10, not SEQ ID NO: 4. Further, as noted above, there are three working examples of fusion proteins described in the specification, not one. These three working examples demonstrated that both SEQ ID NO: 2 and SEQ ID NO: 10 can enhance cell permeability when fused to a polypeptide in a fusion protein. As noted in prior responses, the types of proteins to be fused to the peptides of the invention are also described on page 4 of the specification and represent well known classes of proteins. In the interest of expediting prosecution and allowance, Claim 31 has been amended to further specify that the fusion proteins are not natural HBV surface proteins. The written

description support for this limitation can be found, for example, in original claims 1 and 2 and in the specification on page 3, last paragraph, and in the first three lines of page 5.

The diversity of the working examples, coupled with the description on page 4 is certainly sufficient written description to have put one of ordinary skill in the art on notice that the inventors were in possession of the fusion proteins of claims 31-38. Claims 31-38 each utilize a peptide of claim 30. The specification clearly indicates that the peptides of claim 30 will enhance cell permeability of proteins from diverse classes when fused with these proteins (see page 4). The working examples (Examples 1 and 4) demonstrate that diverse peptides of claim 30 (e.g., SEQ ID NO: 2 and SEQ ID NO: 10) enhance cell permeability when fused to diverse proteins (e.g., the PLAP motif from the cytoplasmic domain of TNF-RI and eGFP). Furthermore, WO 00/46376 and the *Gene Therapy* article described above provide additional confirmation that fusion proteins of the claimed peptides coupled to diverse proteins, can be transported across cell membranes.

Applicants submit that Claims 39-41 were erroneously included in the written description rejection. There was no explanation given in the Office Action of why these claims allegedly lack a written description. Moreover, these claims are directed to subgroups of the isolated 12-mer peptide of claim 30, which was not included in this rejection. Claim 39 is directed to a subgroup of peptides of claim 30 that are described in the specification as subtypes (i.e., variants) of the HBV PreS2-TLM peptide, i.e., SEQ ID NO: 2 (see original Figure 3, as well as the amended description of replacement Figures 3A and 3B in the amendment dated March 16, 2004). Claim 40 is directed to a subgroup of the peptides of claim 30 consisting of fragments of avian HBV proteins (see original Figure 4 and the amended description of replacement Figures 4A and 4B in the amendment dated March 16, 2004). Similarly, claim 41 is directed to a subgroup of the peptides of claim 30 which are fragments of rodent HBV (see original Figure 5 and the amended description of replacement Figure 5 in the amendment dated March 16, 2004).

The specification, on page 2 also clearly indicates that these peptides are part of the present invention. Thus, there is certainly written description support for claims 39-41, and the rejection of these claims should be withdrawn.

Applicants request that the rejection of claims 31-38, be withdrawn as well.

Rejections Based On Anticipation.

Claims 31, 32, and 36 stand rejected as being allegedly anticipated under 35 U.S.C. §102 (b) by Hildt *et al.* (1995 *Oncogene*). This ground for rejection is unwarranted. The *Oncogene* article describes a naturally occurring HBV protein. Claim 31, as currently amended, is directed to a fusion protein that is not a natural HBV protein. This clarifying amendment further states that which is described in the specification. Claims 32 and 36 depend directly on claim 31. Accordingly, claims 31, 32, and 36 can not be anticipated by the applied reference and the rejection should be withdrawn.

Claims 31, 32, and 36 also stand rejected as being anticipated by the protein disclosed in NCBI Accession No. 540642 and by the protein disclosed in NCBI Accession No. 138800. Here too, each of the cited proteins is a natural HBV protein. As stated above, the present claims are directed to fusion proteins that are not natural HBV proteins. Accordingly, these grounds for the rejection for claims 31, 32 and 36 should be withdrawn, as well.

Rejections Based On Obviousness.

Claims 30 and 39 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Hildt *et al.* (1995 *Oncogene*). This rejection is unwarranted, as well. Claim 30 is directed to isolated 12-mer peptides. Claim 39 is directed to a subset of isolated 12-mer peptides of claim 30, which are variants of SEQ ID NO: 2 (i.e., SEQ ID NO: 4, 6, and 8). In assessing whether a claim is obvious over the prior art, it is hornbook law that evidence of unexpected results should be considered as rebutting a *prima facie* case for obviousness.

The Hildt *et al.* article describes a full length HBV surface protein. The 12-mer sequence (SEQ ID NO: 2) that is highlighted in this article was not singled out for its ability to enhance cell permeability, nor was there any suggestion in this article to isolate this 12-mer peptide, for any

purpose. Rather, the reference teaches that this peptide sequence is responsible for dimerization of the protein. One of ordinary skill in the art would not have been motivated to isolate this peptide based on the teachings of the reference.

In this case, the utility of the peptides of claim 30 (including the peptide of SEQ ID NO: 2), rests on the unexpected ability of the claimed peptides to enhance cell permeability. The applied reference does not teach or suggest such cell permeability enhancing activity for SEQ ID NO: 2 of claim 30. One of ordinary skill in the art would not have had a reasonable expectation that the peptides of claim 30 would enhance cell permeability based on the teachings of the reference. Furthermore, the peptides of claim 39 include SEQ ID NO: 4, SEQ ID NO: 6, and SEQ ID NO: 8, but not SEQ ID NO: 2. There is no teaching or suggestion, whatsoever, in the Hildt *et al.* article for the peptides of claim 39. Accordingly, neither claim 30 nor claim 39 would have been obvious to one of ordinary skill in the art based on this reference. The rejection of claims 30 and 39 on the grounds of obviousness should be withdrawn.

Conclusion.

Applicants request reconsideration of the finality of the present rejection. Claims 30-41 are patentable under 35 U.S.C. §112 and over the applied art. Early allowance of all claims and passage of the application to issue is solicited. In the event the foregoing is deemed unpersuasive, applicants request that the present amendment be entered of record to place the application in better form for Appeal.

Respectfully submitted,

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